

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-203

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION:	NDA 22-203	TRADE NAME:	Astepro® Nasal Spray
APPLICANT/SPONSOR:	Meda Pharmaceuticals	USAN NAME:	Azelastine hydrochloride
MEDICAL OFFICER:	Susan Limb, MD		
TEAM LEADER:	Sally Seymour, MD	CATEGORY:	Antihistamine
REVIEW DATE:	October 8, 2008	ROUTE:	Intranasal inhalation

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
August 14, 2008	August 15, 2008	N017	Class 1 resubmission for adult SAR indication following dispute resolution

REVIEW SUMMARY: This is a medical officer review of labeling submitted for Astepro® Nasal Spray following a Not Approvable action the first cycle and subsequent dispute resolution. Astepro Nasal Spray is an antihistamine nasal spray that contains 0.1% azelastine hydrochloride with sucralose and sorbitol. Astepro is a new formulation developed by MEDA to address the bitter taste of the currently marketed azelastine nasal spray, Astelin Nasal Spray. NDA 22-203 for Astepro was first submitted on July 30, 2007, with the following proposed indications: 1) treatment of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older at 1 or 2 sprays per nostril twice daily; 2) treatment of the symptoms of SAR in patients 5 to 11 years of age at 1 spray per nostril twice daily; and 3) treatment of the symptoms of vasomotor rhinitis (VMR) in patients 12 years of age and older at 2 sprays per nostril twice daily. The proposed indications were the same as the approved indications for the original, unsweetened intranasal formulation of azelastine, Astelin® Nasal Spray.

NDA 22-203 was reviewed and a Not Approval action was taken (May 30, 2008). Details of the original clinical review can be found in the attached primary medical officer's review dated February 29, 2008. The Not Approval letter cited the following clinical deficiencies: 1) pediatric indication not supported in patients 5 to 11 years of age; 2) _____ in patients with vasomotor rhinitis (VMR); and 3) _____

The Applicant requested a formal dispute resolution on July 1, 2008. A dispute resolution meeting with the Applicant was held on July 28, 2008. The Applicant stated that comparability between Astepro and Astelin had been demonstrated, and on the basis of comparability, the indications and dosing recommendations approved for Astelin should also be approved for Astepro. After deliberation, Dr. Curtis Rosebraugh, Director of the Office of Drug Evaluation II, Center for Drug Evaluation and Research, supported the Applicant's request for approval of the SAR indication in patients 12 years and older. However, Dr. Rosebraugh supported DPAP's findings that the application lacked sufficient data to support the SAR indication in patients 5 to 11 years, the VMR indication in patients 12 years of age and older, and an _____ . A detailed discussion of the dispute resolution is found in the copy of Dr. Rosebraugh's Response to a Formal Dispute Resolution Appeal attached to this document.

In this resubmission, the Applicant submitted proposed labeling for Astepro for the SAR indication in patients 12 years of age and older, including caveats against use in patients under the age of 12 years. The VMR indication _____ information have also been removed. These changes are appropriate and consistent with the deficiencies in the NA letter and decision from the Dispute Resolution. Additional minor changes suggested by the review team have been incorporated in the labeling, including clarification of the findings in the QT study (Section 12.2), minor wording and typographical edits, and updates to the carton/container label. The suggested edits can be found highlighted in the attached label. Of note, Section 6, Adverse Reactions, is based on data from a completed 2-week safety and efficacy trial and the 6-month interim report of a 1-year safety study. The Applicant has agreed to submit the final study report in January 2009 at which time this section of the label will be updated to include 12-month safety data.

Assuming acceptance of the labeling revisions and no further changes to the proposed label, the Class I resubmission is recommended for Approval.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: ☒ APPROVAL ☐ COMPLETE RESPONSE

I. Summary

Meda submitted a 505(b)(1) new drug application (NDA# 22-203) on July 30, 2007, for a sweetened azelastine nasal spray for the treatment of symptoms of seasonal allergic rhinitis (SAR) in patients 5 years of age and older and for the treatment of vasomotor rhinitis (VMR) in patients 12 years of age and older. The proposed dosing regimen is 1-2 sprays twice daily. An unsweetened azelastine nasal spray is currently approved for the same indications (NDA# 20-114, Meda) under the tradename Astelin Nasal Spray, but because of the bitter taste, Meda developed the proposed sweetened formulation, which contains the additional excipients, sucralose and sorbitol.

A Not Approval was taken on NDA# 22-203 on May 30, 2008, with the following clinical deficiencies (paraphrased): 1) pediatric indication not supported because of '_____ b(4)
— in patients 5 to 11 years of age; 2) _____ in patients with
vasomotor rhinitis (VMR); and 3) _____

The clinical program conducted by MEDA was based upon a comparability approach with Astepro Nasal Spray and Astelin Nasal Spray. Details of the original clinical review can be found in the primary medical officer's review dated February 29, 2008. Of note, the original clinical review recommended an Approval action for the SAR indication in patients 12 years of age and older on the basis of the safety and efficacy demonstrated in the pivotal study and the previous studies for Astelin Nasal Spray. A Not Approval action was recommended for the SAR indication in patients 5 to 11 years of age and the VMR indication. The original review also concluded that an _____ for SAR was not supported. These b(4)
recommendations were made at the time of the review in anticipation of an administrative decision to split the proposed indications and on the presumption that agreement would be made on labeling. However, at the time of the action, no agreement on labeling had been reached and a Not Approval letter was issued as outlined above. The Not Approval action recommended by the larger clinical team was consistent with the primary medical officer's recommendations. In addition, the primary medical officer's review came to the conclusion that Astepro and Astelin were comparable, whereas subsequent clinical reviews have concluded that comparability was not demonstrated. Comparability is not a clearly defined concept as applied to nasal spray products. The original assessment of comparability made in the initial clinical review was not based on a formal definition of comparability, such as the definition presented in the Draft Guidance on Allergic Rhinitis, April 2000, or the Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action, April 2003. When criteria from either of these guidances are applied to the Astepro data, comparability between Astepro and Astelin is not demonstrated.

The Applicant requested a formal dispute resolution on July 1, 2008. A dispute resolution meeting with the Applicant was held on July 28, 2008. The Applicant stated that comparability between Astepro and Astelin had been demonstrated, and on the basis of

comparability, the indications and dosing recommendations approved for Astelin should also be approved for Astepro. After deliberation, Dr. Curtis Rosebraugh, Director of the Office of Drug Evaluation II, Center for Drug Evaluation and Research, supported the Applicant's request for approval of the SAR indication in patients 12 years and older. However, Dr. Rosebraugh supported DPAP's findings that the application lacked sufficient data to support the SAR indication in patients 5 to 11 years, the VMR indication in patients 12 years of age and older, and _____. A detailed discussion of the dispute resolution is found in the copy of Dr. Rosebraugh's Response to a Formal Dispute Resolution Appeal attached to this document. b(4)

In this resubmission, the Applicant submitted proposed labeling for Astepro for the SAR indication in patients 12 years of age and older, including caveats against use in patients under the age of 12 years. The VMR indication and _____ information have also been removed. These changes are appropriate and consistent with the deficiencies in the NA letter and decision from the Dispute Resolution. Additional minor changes suggested by the review team have been incorporated in the labeling, including clarification of the findings in the QT study (Section 12.2), minor wording and typographical edits, and updates to the carton/container label. The suggested edits can be found highlighted in the attached label. Of note, in Section 6, Adverse Reactions, is based on data from a completed 2-week safety and efficacy trial and the 6-month interim report of a 1-year safety study. The Applicant has agreed to submit the final study report in January 2009 at which time this section of the label will be updated to include 12-month safety data. b(4)

II. Attachments

1. Proposed labeling for Astepro Nasal Spray
2. Dr. Susan Limb's Medical Officer Review of NDA# 22-203, dated February 29, 2008
3. Response to Request for Formal Dispute Resolution, dated August 7, 2008

16 Page(s) Withheld

☐ Trade Secret / Confidential (b4)

☒ Draft Labeling (b4)

☐ Draft Labeling (b5)

☐ Deliberative Process (b5)

Withheld Track Number: Medical- 1

CLINICAL REVIEW

Application Type NDA
Submission Number 22-203
Submission Code N000

Letter Date July 30, 2007
Stamp Date July 30, 2007
PDUFA Goal Date May 30, 2008

Reviewer Name Susan Limb, MD
Review Completion Date February 29, 2008

Established Name Azelastine hydrochloride (sweetened)
(Proposed) Trade Name
Therapeutic Class Intranasal antihistamine
Applicant Medpointe Pharmaceuticals

b(4)

Priority Designation S

Formulation Intranasal solution
Dosing Regimen 1 or 2 sprays each nostril BID
Indication Seasonal allergic rhinitis
Intended Population Patients 5 years of age and older

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	4
1.1	Recommendation on Regulatory Action.....	4
1.2	Risk Benefit Assessment	5
1.3	Recommendations for Postmarketing Risk Management Activities	5
1.4	Recommendations for other Post Marketing Study Commitments	5
2	INTRODUCTION AND REGULATORY BACKGROUND.....	6
2.1	Product Information.....	6
2.2	Tables of Currently Available Treatments for Proposed Indications.....	7
2.3	Availability of Proposed Active Ingredient in the United States	7
2.4	Important Safety Issues With Consideration to Related Drugs	7
2.5	Summary of Presubmission Regulatory Activity Related to Submission.....	8
2.6	Other Relevant Background Information	9
3	ETHICS AND GOOD CLINICAL PRACTICES	9
3.1	Submission Quality and Integrity	9
3.2	Compliance with Good Clinical Practices	9
3.3	Financial Disclosures.....	10
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	10
4.1	Chemistry Manufacturing and Controls	10
4.2	Clinical Microbiology.....	10
4.3	Preclinical Pharmacology/Toxicology	10
4.4	Clinical Pharmacology	11
4.4.1	Mechanism of Action.....	11
4.4.2	Pharmacodynamics	11
4.4.3	Pharmacokinetics	11
5	SOURCES OF CLINICAL DATA	13
5.1	Tables of Clinical Studies	13
5.2	Review Strategy.....	13
5.3	Discussion of Individual Studies	14
5.3.1	Study MP430	14
5.3.2	(b) (4)	15
5.3.3	Study MP432	16
6	REVIEW OF EFFICACY	16
6.1	Indication – Seasonal allergic rhinitis.....	18
6.1.1	Methods	18
6.1.2	Demographics	18
6.1.3	Patient Disposition.....	19
6.1.4	Analysis of Primary Endpoint.....	20
6.1.5	Analysis of Secondary Endpoints	20
6.1.6	Other Endpoints	21
6.1.7	Subpopulations	21
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	21
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	22
6.1.10	Additional Efficacy Issues/Analyses.....	22
7	REVIEW OF SAFETY	22
7.1	Methods	23

7.1.1	Clinical Studies Used to Evaluate Safety	23
7.1.2	Adequacy of Data	23
7.1.3	Pooling Data Across Studies to Estimate and Compare Incidence	24
7.2	Adequacy of Safety Assessments	25
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	25
7.2.2	Explorations for Dose Response.....	27
7.2.3	Special Animal and/or In Vitro Testing.....	27
7.2.4	Routine Clinical Testing	27
7.2.5	Metabolic, Clearance, and Interaction Workup	27
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	27
7.3	Major Safety Results	28
7.3.1	Deaths	28
7.3.2	Nonfatal Serious Adverse Events	28
7.3.3	Dropouts and/or Discontinuations	28
7.3.4	Significant Adverse Events.....	29
7.3.5	Submission Specific Primary Safety Concerns.....	29
7.4	Supportive Safety Results.....	29
7.4.1	Common Adverse Events	29
7.4.2	Laboratory Findings.....	31
7.4.3	Vital Signs	31
7.4.4	Electrocardiograms (ECGs).....	31
7.4.5	Special Safety Studies.....	32
7.4.6	Immunogenicity	32
7.5	Other Safety Explorations	32
7.5.1	Dose Dependency for Adverse Events.....	32
7.5.2	Time Dependency for Adverse Events	32
7.5.3	Drug-Demographic Interactions	32
7.5.4	Drug-Disease Interactions.....	32
7.5.5	Drug-Drug Interactions.....	33
7.6	Additional Safety Explorations.....	33
7.6.1	Human Carcinogenicity	33
7.6.2	Human Reproduction and Pregnancy Data	33
7.6.3	Pediatrics and Effect on Growth	33
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	34
7.7	Additional Submissions.....	34
8	POSTMARKETING EXPERIENCE.....	34
9	APPENDICES	34
9.1	Literature Review/References	34
9.2	Labeling Recommendations	34
9.3	Advisory Committee Meeting	35
10	INDIVIDUAL STUDY REVIEWS.....	36